عنوان المشروع باللغة العربية	تصميم تويولين ملزمة العلاج الكيميائي لتنظيم ديناميات أنيبيب
عنوان المشروع باللغة الإنجليزية	Designing tubulin binding chemotherapy agents for regulating microtubule dynamics
المشرف الرئيس	Md Ashrafuzzaman
التخصص الدقيق للمشرف الرئيس	Biophysics
المشرف المساعد	Seema Zargar
المدة المتوقعة لإنجاز البحث منذ الحصول على موافقة عمادة الدراسات العليا	8 months
Abstract or synopsis of the proposal (200 words or less):	A drug design template will be developed based on target binding energetics. We propose to merge our aptamer design technologies (i) entropy fragment based approach (EFBA) and (ii) screened Coulomb interaction based approach (SCIA) to create a universal drug design platform (DDP). We shall use this novel platform to design tubulin binding chemotherapy drugs (TBCDs). The univers al DDP will allow us to discover microtubule destabilizing colchicine derivatives, stabilizing taxol derivatives, general aptamers to bind to specific tubulin structures. Microtubule-targeting agents suppress microtubule dynamics, cause cell division disruption and induce cell death. The microtubule assembly by αβ-tubulin dimer polarization is expected to be regulated by TBCD. These agents are therefore predicted as important chemotherapy drugs that ultimately create actions to regulate cell division. We expect specifically to discover a set of colchicine derivative based TBCDs. New derivatives will be designed by mainly structural modifications in parent colchicine compound and changing its charge group properties. We shall evaluate the designs using a series of in silico and in vitro model studies. As cell membrane based toxicity of drugs is evident, a cytotoxicity assay will be developed to assess the CDs cell surface binding and thus address the drugs' possible off t arget cytotoxicity.
Hypothesis or scientific justification of the proposal	1. Merging EFBA and SCI techniques a universal drug design platform (DDP) can be created 2. Universal DDP will help us design a set of tubulin binding novel colchicine based derivatives 3. In silico binding assays are quite powerful to address the target tubulin binding potency of novel colchicine derivatives and raise clarification on statistical binding energetics 4. Cell surface binding of colchicine drugs helps us understand the drugs' off target binding as well as drug cytotoxicity. In cell surface the colchicine binding phenomena will be inspected using atomic force microscopy phase diagram thus the possible cytotoxicity of the colchicine drug will be addressed.

Specific objectives	1. Discover a universal drug design platform 2. Design colchicine derivatives as tubulin binding agents. 3. Discover chemotherapy drugs targeting tubulin structure with novel colchicine derivatives. 4. Address cell surface binding of colchicine and thus discover the possible source of cytotoxicity usually reported in chemotherapy applications of drugs.
Methodology & Major Techniques to be used	Plan The proposed plan consists of four phases. They integrate in house computational and experimental techniques to accomplish the goal. Phase I. This phase will create a universal drug design platform by merging our aptamer design technologies EFBA and SCIA. We will then apply our universal drug design technology to design novel colchicine derivatives for binding with specific tubulin monomer. Phase II. After designing phase (phase I) we shall perform phase II in silico investigation including molecular dynamic (MD) simulations or numerical computation and bioinformatics to study target binding properties of designed novel derivatives in molecular level. With the top candidates selected from these investigations, we shall then proceed to utilizing one of our patented direct detection methods (DDMs) to assess the strength of drug binding with tubulin through inspection of binding energetics and finalize the optimal drug candidate. Phase III. We then would conduct various functional studies on the finalized optimal drug candidate(s) using in silico approach before planning for in vivo studies (to be conducted in another future M.Sc. project). This study will provide further insights on the impact of the optimal TBCD candidate for tubulin binding. It also allows us to detect the effective functional groups in the TBCD structure, perform necessary modifications in these functional groups and further reengineer the template to ensure optimal regulation of microtubule assembly via tubulin monomer binding. Phase IV. We shall then inspect the drugs cell membrane binding energetics through studying the statistical mechanical nature of the drugs' cell surface adsorption mechanisms. This will be performed inspecting the atomic force microscopy phase diagrams of colchicine incubated cancer cells.
Availability of Samples	YES
If the answer is no, kindly justify	
Availability of Chemicals	YES
If the answer is no, kindly justify	
Availability of	YES

Instruments	
Availability of Ethical Approval (if needed)	YES
Recent References	Md. Ashrafuzzaman, C.-Y. Tseng, J. Kapty, J. Mercer, J. Tuszynski, A computationally designed DNA aptamer template with specific binding to phosphatidylserine, Nucleic Acid Therapeutics (2013), 23, 418-26. Md. Ashrafuzzaman*, J. Tuszynski, Ion pore formation in lipid bilayers and related energetic considerations, Curr. Med. Chem. (2012), 19, 1619-1634. Md. Ashrafuzzaman* and J. Tuszynski, Regulation of channel function due to coupling with a lipid bilayer, J. Comput. Theor. Nanosci. (2012) 564-570. Md. Ashrafuzzaman*, C.-Y. Tseng, J. Tuszynski, Regulation of channel function due to physical energetic coupling with a lipid bilayer, Biochem. Biophys. Res. Comm. (2014), 445, 463-468. Aptamers as both drugs and drug-carriers. Biomed. Res. Int. (2014), Article ID 697923, 21 pages.